

U.S. Pat. App. Ser. No. 10/622,126
Docket No. 056754/0125184
Amendment and response to 4/11/2006 Office Action

REMARKS

Claims 1-50 are pending in the application. Claims 1-37 and 43-50 are withdrawn as being directed to non-elected inventions. In the Office Action mailed April 11, 2006, claims 38-42 are rejected under 35 U.S.C. 112, first paragraph as failing to comply with the written description requirement. Claims 38, 39, and 41 are rejected under 35 U.S.C. 102(b) as being anticipated by Guatelli et al., *Clinical Microbiology Reviews* 2:217-226 (1989) (hereinafter "Guatelli"). Claims 38-42 are rejected under 35 U.S.C. 102(a) as being anticipated by Hamad-Schifferli et al., *Nature* 415:152-155 (2002) (hereinafter "Hamad-Schifferli"). The Abstract is objected to under 37 C.F.R. 1.72 as not being descriptive of the elected invention.

I. Objection to the Abstract Under 37 C.F.R. 1.72

The Abstract is objected to under 37 C.F.R. 1.72 as not being descriptive of the elected invention. The Applicants have amended the Abstract to specifically describe the currently elected invention. Support for this amendment is found in the Specification at least at paragraphs [0005], [0035]-[0036], [0044], and [0063]-[0064], in Figs. 1, 2, and 3B, and in original claims 38-42. The Applicants have also amended paragraph [0008] to correct a typographical error. No new matter is added by these amendments. Entry of these amendments and withdrawal of the objection to the Abstract is therefore respectfully requested.

II. Rejections under 35 U.S.C. 112, first paragraph

Claims 38-42 are rejected under 35 U.S.C. 112, first paragraph as failing to comply with the written description requirement. Specifically, the Examiner has stated that the claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. In particular, the Examiner has asserted that (1) the Applicants have not shown that the required atomic resolution for surface immobilized components, and in particular the ability to apply energy inputs and to react a molecular unit onto a substrate at a desired location, can be achieved and (2) the Applicants have not shown that

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the controlled movement required by the Applicants' invention can be achieved with the required level of precision.

The Applicants respectfully traverse the rejection. As noted by the Examiner, the knowledge possessed by those skilled in the art may be established by referencing to patents and publications available to the public (e.g., *In re Lange*, 644 F.2d 856, 863, 209 USPQ 288, 294). The Applicants submit that, at the time of filing the present application, those of skill in the art of the invention had already shown that all of the component structures and technologies required for the Applicants' invention were feasible, including both the ability to apply energy inputs and react a molecular unit onto a substrate at a desired location and the controlled movement required by the Applicants' invention.

With respect to the required atomic resolution for surface immobilized components, and in particular the ability to apply energy inputs and to react a molecular unit onto a substrate at a desired location, the Applicants respectfully submit that numerous examples existed in the literature prior to the filing of the Applicants' priority application. For example, Gartner et al. had previously demonstrated that individual molecules can be positioned precisely in solution to drive a specific reaction (Gartner, Zev J. et al., "The Generality of DNA-Templated Synthesis as a Basis for Evolving Non-Natural Small Molecules", *J. Am. Chem. Soc.*, 6/22/2001, 6961-6963, 123; hereinafter "Gartner I"). In Gartner I, it was demonstrated that DNA-templated synthesis is capable of supporting a range of reaction types and is not limited to the creation of structures resembling nucleic acid backbones, suggesting DNA's potential in directing, rather than simply encoding, a range of synthetic reactions.

Similarly, scaffolds for driving programmable reactions were well-known. For example, Jacobsen et al. had previously demonstrated the technique of genetically modifying a polyketide synthase in order to produce a desired drug target (Jacobsen, John R. et al., "Precursor-Directed Biosynthesis of Erythromycin Analogs by an Engineered Polyketide Synthase", *Science*, 7/18/1997, 367-369, 277; hereinafter "Jacobsen"). In Jacobsen, chemically synthesized, cell-permeable, non-natural precursors were transformed into molecules resembling natural products by genetically engineered polyketide synthases.

Further, Hamad-Schifferli et al. had previously demonstrated that a functional device using an external input was possible at the time of the filing of the application. In Hamad-

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Schifferli, remote electronic control over the hybridization behavior of DNA molecules is achieved by inductive coupling of a radio-frequency magnetic field to a metal nanocrystal covalently linked to DNA [Hamad-Schifferli at page 152, col. 2]. In particular, the work of Hamad-Schifferli demonstrates that individual nanocrystals can be removed while leaving surrounding molecules unaffected, which reaction is also fully reversible.

In light of the foregoing literature, as well as other literature and studies not cited, the Applicants respectfully submit that the ability to precisely apply inputs and react a molecular unit onto a substrate at a desired location was feasible utilizing technology known in the art at the time of the filing of the Applicants' priority application. The Examiner particularly notes that the teachings of Ge and Demers do not show molecular resolution on the angstrom level scale. The Applicants respectfully submit that the fact that two references do not happen to show what the Examiner asserts to be the required level of resolution does not preclude existence of, nor supercede, other contemporaneous publications and studies, such as those discussed above, that had demonstrated the feasibility of the technology and the knowledge of one of ordinary skill in the art at the time of filing of the Applicants' priority application.

With respect to the ability to achieve the controlled movement required by the Applicants' invention, many examples existed at the time of filing of the priority application, including the particular examples of motor proteins like kinesin and myosin (structures that move in steps). For example, Hess et al. had previously disclosed user control of the motion of a kinesin motor enzyme by triggering its ATP fuel source (Hess, H. et al., "Light-Controlled Molecular Shuttles made from Motor Proteins Carrying Cargo on Engineered Surfaces", *Nano Letters*, Vol. 1, No. 5, 235-239, 10 January 2002; hereinafter "Hess"). In Hess, microtubules, covalently loadable with cargo, were moved on engineered kinesin tracks. Hess in particular notes that these structures are useful as components "for the construction of nanoscale assembly lines."

Furthermore, there had been, at the time of filing of the priority document for the present application, numerous publications describing work demonstrating precise control of molecular shuttles using a myriad of input sources. A recent publication by Chatterjee et al., Chatterjee, Manashi N. et al., "Beyond switches: Ratcheting a Particle Energetically Uphill with a Compartmentalized Molecular Machine", *J. Am. Chem. Soc.*, 2006, 4058-4073, 128, contains

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footnotes that are very helpful in putting in context the knowledge of the art with respect to control of molecular shuttles at the time of the filing of the Applicants' priority application. These footnotes list many different papers, cumulative of references already of record and therefore not individually submitted in a disclosure statement, that were either published before, or describe work performed contemporaneously with, the filing date of the present application, including papers describing photochemically responsive molecular shuttles (footnote 13), electrochemically responsive molecular shuttles (footnote 15), chemically responsive molecular shuttles (footnote 16), and pH-responsive molecular shuttles (footnote 17) [Chatterjee at pages 4060-4061].

In light of the foregoing, the Applicants respectfully submit that the controlled movement required by the Applicants' invention was feasible utilizing technology known in the art at the time of the filing of the Applicants' priority application, and that such technology was known to one of ordinary skill in the art of the invention. The Examiner has particularly asserted that Hamad-Schifferli "does not show the 'shifting' as claimed by Applicants". The Applicants respectfully note that the teaching of Hamad-Schifferli, on which one of the Applicants is co-listed as an author, is not directed toward a molecular assembly line or shuttle, but is rather directed toward the demonstration of the other of the two component technologies put at issue by the Examiner- specifically, the ability to apply energy inputs and to react a molecular unit onto a substrate at a desired location. There would therefore be no reason for the teaching of Hamad-Schifferli to demonstrate anything resembling "shifting", as has been posited by the Examiner.

The results discussed above, when coupled with the results regarding the ability to precisely apply inputs and react a molecular unit onto a substrate at a desired location that had been obtained by the likes of Gartner, Jacobsen, Hamad-Schifferli and others, therefore amply demonstrate that a functional molecular assembly line according to the invention of the Applicants was possible at the time of the filing of the application, that all of the component technologies of the Applicants invention were both possible and understood by those of ordinary skill in the art of the invention, and that the Applicants were fully in possession of the invention.

That the component technologies employed in the Applicants' invention were well understood in the art at the time of filing of the application is further confirmed by later publications that describe similar and related work being performed by others at the time of the

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Applicants' filing. For example, Gartner et al. continued and extended their earlier work (Gartner I), publishing a paper, submitted contemporaneously with the Applicant's priority filing, that describes work demonstrating that DNA can be used to template very specific reactions, i.e. that linear assemblies can selectively scaffold molecular reactions by physical confinement (Gartner, Zev J. et al., "Multistep Small-Molecule Synthesis Programmed by DNA Templates", *J. Am. Chem. Soc.*, 2002, 10304-10306, 124; hereinafter "Gartner II"). In Gartner II, several multistep DNA-templated small molecule syntheses employing multiple linker strategies were demonstrated.

Futhermore, Reif contemporaneously demonstrated a working molecular walker utilizing DNA strands as chemical fuel or inputs (Reif, John H., "The design of autonomous DNA nanomechanical devices: Walking and rolling DNA" *Natural Computing*, 2003, 439-461, 2; hereinafter "Reif"). In Reif, nanomechanical devices are demonstrated that execute cycles of unidirectional translational movement without external environmental changes. Reif teaches that, because DNA hybridization is competitive, the fuel effectively biases the motion to a stable position, as in the invention of the Applicants. Further, because DNA can have orthoganol sequences, specific/unique locations along the chain can therefore be targeted chemically.

The Examiner notes that, in the Specification, the Applicants state that "a molecular assembly line has yet to be constructed". The Applicants respectfully respond that the statement is made in the Background section of the Specification and is merely an assertion of the novelty of the Applicants' invention over the prior art. It would be inconsistent with the requirements of the patent statutes, as well as being impossible to achieve, to simultaneously require an invention to be both novel and to also have been previously made by others. The Examiner further notes that there is no working example of the claimed invention. The Applicants respectfully respond that it is well-established that production of a working example of an invention is not required for patentability. Under 37 C.F.R. 1.131, the filing of a patent application meeting the requirements of 35 U.S.C 112 operates as a constructive reduction to practice and is sufficient to establish possession of the invention.

The Applicants respectfully submit that they have met their burden under 35 U.S.C 112, in that the foregoing and other references published prior to the Applicants' filing date demonstrate that, at the time of the filing of the present application, there was a widespread

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knowledge in the art of the invention of means of implementing all of the underlying technologies and concepts employed by the Applicants' invention, including the required atomic resolution for surface immobilized components, in particular the ability to apply energy inputs and to react a molecular unit onto a substrate at a desired location, and the required precision of controlled movement. That this knowledge was available to one of ordinary skill in the art of the invention is further correlated by the many later-published references that demonstrate that work was being done by others, contemporaneously with the work of the Applicants, that employed and built on the same concepts and technologies employed by the Applicants' invention. This wide-spread knowledge in the art demonstrates that the claimed invention is described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention and that the disclosure of the Applicants provides sufficient written description support for the claimed invention. Reconsideration and withdrawal of the rejections of claims 38-42 under 35 U.S.C. 112, first paragraph is therefore respectfully requested.

III. Rejections under 35 U.S.C. 102(b)

Claims 38, 39, and 41 are rejected under 35 U.S.C. 102(b) as being anticipated by Guatelli. The Applicants respectfully traverse the rejection. Guatelli does not disclose the invention of the Applicants, as it fails to disclose the translatable molecular shuttle, responsive to an input signal, of the Applicants' invention. The Applicants' invention employs a molecular shuttle that translates between the binding positions along a molecular chain by means of sequentially breaking and forming bonds between the molecular chain subunits and the shuttle in response to at least one input signal. [Specification at least at paragraphs [0005], [0035]-[0036], [0044], and [0063]-[0064] and in Figs. 1, 2, and 3B].

In contrast, as noted by the Examiner, Guatelli teaches an operational polymerase. The individual polymerase molecules of Guatelli do not sequentially break and form bonds between subunits of the DNA chain in response to an input signal. Moreover, polymerase reactions do not operate by the translation of individual polymerase molecules along the DNA chain. The rate of polymerase reaction is related to the concentration of polymerase molecules in solution, with different molecules operating at different points of the DNA chain, rather than through the

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translation of a single molecule along the length of the entire chain. Guatelli therefore fails to show the translatable molecular shuttle of the Applicants' invention.

In order to more distinctly claim and point out these aspects of the Applicants' invention, the Applicants have herein amended independent claim 38 in order to call out that the shuttle of the Applicants' invention is a translatable molecular shuttle capable of translating along the molecular chain by means of sequentially breaking and forming bonds between the molecular subunits and the shuttle in response to one or more input signals and that the shuttle translates between the binding positions. Support for this amendment is found in the Specification at least at paragraphs [0005], [0035]-[0036], [0044], and [0063]-[0064] and in the Drawings in Figs. 1, 2 and 3B. As discussed above, a molecular shuttle that translates along the molecular chain between the binding positions by means of sequentially breaking and forming bonds between the molecular subunits and the shuttle in response to one or more input signals is not shown in Guatelli, nor is it shown in any other art of record. Guatelli therefore fails to disclose or make obvious the Applicants' invention, whether taken alone or in combination, as does all other art of record. Entry of the amendment, reconsideration and withdrawal of the rejections of claim 38, and allowance of claim 38, as amended, is therefore respectfully requested.

Because claims 39 and 41 depend from currently amended independent claim 38, which is in condition for allowance, the Applicants believe that claims 39 and 41 are also in condition for allowance. Reconsideration and withdrawal of the rejection of claims 39 and 41 as being anticipated by Guatelli is therefore also respectfully requested.

IV. Rejections under 35 U.S.C. 102(a)

Claims 38-42 are rejected under 35 U.S.C. 102(a) as being anticipated by Hamad-Schifferli. The Applicants respectfully traverse the rejection. Hamad-Schifferli does not disclose the invention of the Applicants, as it fails to disclose the molecular shuttle, responsive to an input signal, of the Applicants' invention. As previously discussed, the Applicants' invention employs a translatable molecular shuttle that translates between the binding positions along a molecular chain by means of sequentially breaking and forming bonds between the molecular chain subunits and the shuttle in response to at least one input signal. In contrast, Hamad-Schifferli teaches remote electronic control over the hybridization behavior of DNA molecules, by inductive coupling of a radio-frequency magnetic field to a metal nanocrystal covalently

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linked to DNA [Hamad-Schifferli at page 152, col. 2]. As noted by the Examiner, the “shuttle” of Hamad-Schifferli, to the extent it can be considered a shuttle, *diffuses* through the solution and aligns itself on another strand of DNA. The “shuttle” of Hamad-Schifferli therefore *does not translate between the binding positions along a single molecular chain by means of sequentially breaking and forming bonds between the molecular chain subunits and the shuttle*. Hamad-Schifferli therefore fails to show the translatable molecular shuttle of the Applicants’ invention. This deficiency of Hamad-Schifferli is not cured by any other art of record.

As described in Section III of this Response, the Applicants have herein amended independent claim 38 in order to call out that the shuttle of the Applicants’ invention is a translatable molecular shuttle capable of translating along the molecular chain by means of sequentially breaking and forming bonds between the molecular subunits and the shuttle in response to one or more input signals and that the shuttle translates between the binding positions. As discussed above, a molecular shuttle that translates along the molecular chain between the binding positions by means of sequentially breaking and forming bonds between the molecular subunits and the shuttle is not shown in Hamad-Schifferli, nor is it shown in any other art of record. Hamad-Schifferli therefore fails to disclose or make obvious the Applicants’ invention, whether taken alone or in combination, as does all other art of record. Entry of the amendment, reconsideration and withdrawal of the rejections of claim 38, and allowance of claim 38, as amended, is therefore respectfully requested.

Because claims 39-42 depend from currently amended independent claim 38, which is in condition for allowance, the Applicants believe that claims 39-42 are also in condition for allowance. Reconsideration and withdrawal of the rejection of claims 39-42 as being anticipated by Hamad-Schifferli is therefore respectfully requested.

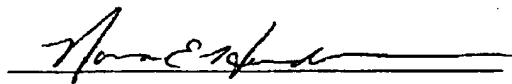
V. Conclusion

Claim 38 has been amended to more clearly and distinctly point out the Applicants’ invention. The Abstract has been amended to allow the public generally to determine quickly from a cursory inspection the nature and gist of the elected invention. Paragraph [0008] of the Specification has been amended to correct a typographical error. No new matter is presented by these amendments. The Applicants respectfully submit that claims 38-42 are now in condition

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for allowance, which action is now requested. For this reason, and in view of the foregoing arguments, the Applicants believe that this application is now in condition for allowance, which action is earnestly solicited. Should there remain any unresolved issues, it is respectfully requested that the Examiner telephone Norma E. Henderson, Applicants' Attorney, at 603-437-4400, so that such issues may be resolved as expeditiously as possible.

Respectfully Submitted,



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